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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,329	12/10/2005	Jung Moon Kim	4240-138	9719

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
MACFARLANE, STACEY NEE	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,329	KIM ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/10/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-20 and 23-29* is/are pending in the application.

4a) Of the above claim(s) *10-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-9, 18-20 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 10, 2008 has been entered.

Response to Amendment

2. Claim 1 has been amended and claim 29 newly added as requested in the amendment filed on October 10, 2008. Following the amendment, claims 1, 2, 5-20 and 23-29 are pending in the instant application.

Claims 10-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on July 23, 2007.

Claims 1, 2, 5-9, 18-20 and 23-29, in so far as they are drawn to the elected species of: BMPs, SEQ ID NO: 1, SEQ ID NO: 14, TAT and TGF-β are under examination in the instant office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed on October 10, 2008 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-9 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/197867 A1 (2004) (hereafter "the '867 publication"), and further in view of US Patent 5,013, 649 (1991), and Leighton et al. (2003) (all previously cited) for reasons of record in the Office Action mailed September 27, 2007.

Claims are drawn to a polypeptide containing (a) a protein transduction domain (PTD) comprising the instantly-elected TAT, (b) a furin activation domain (FAD) comprising the instantly-elected SEQ ID NO: 14, and (c) a non-activated tissue regulation domain (TRD) comprising the instantly-elected SEQ ID NO: 1, which is activated by the proprotein convertase cleavage and which stimulate the formation or regeneration of tissues. Dependent claims recite , wherein the proprotein convertase is

furin; wherein the TRD to be cleaved by proprotein convertase is the instantly-elected BMPs (bone morphogenic proteins); the polypeptide is in the form of PTD, FAD and TRD; the tissue is bone or cartilage and further comprising the instantly-elected growth factor TGF-β.

In Remarks filed October 0, 2008, Applicant traverses the rejection on the following grounds. At page 8, paragraphs 2 and 3, Applicant states that Claim 1 has been amended to include a recitation of the structure as having a linear structure and states,

> "the claims are not simply structural recitations, but also comprise functional description, where the TRP is activated by cleavage of the FAD and which stimulates the growth or formation of tissues or to induce the regeneration of tissues. Therefore structural recitations that are similar to those of the claims, but do not possess the claimed activity are not encompassed by the claims. Similarly, cited references showing a similar structure must also possess the recited function in order to render the claimed invention obvious."

Applicant traverses the rejection over the prior art polypeptides on the grounds that the physical and chemical properties of the claimed invention are distinct because "Claim 1 has been amended to clarify that the claimed TRPs have a linear structure and do not require the 3D structure of the prior art BMPs" (page 9, paragraph 1). On page 11 of Remarks, Applicant argues that,

> "Most proteins expressed from prokaryotic organisms form biologically inactive inclusion bodies. There have been many efforts made to induce restructuring/refolding of these proteins to achieve the physical and chemical characteristics of native protein, but it is very difficult to induce such. The present invention, however, provides solution to both the need for a biologically active protein and the need to be able to produce such from a prokaryotic organism and therefore provides a polypeptide that may be used in commercial processes. The biologically inactive polypeptide is produced from a prokaryotic organism (E. coli, using 8M Urea) and is denatured/unfolded into a linear structure, in order to

> maximize surface energy. This structure is shown in the application at Example 7 and in Figs. 21-23, 28, and 29."

The protein's linear structure comes from the method of making in which the polypeptide is denatured/unfolded into a linear structure and this method overcomes problems common in commercial polypeptide production. Applicant further argues that such denaturation produces polypeptides that,

> "have no original 3-dimentional structure and therefore no biological activity and do not bind the BMP receptor of cell membrane" (page 11, paragraph 2).

It should be noted that the indication that the polypeptides of the claims have no biological activity potentially raises issues of utility under 35 USC 101, however, the art teaches essentially identical protein structures are of value in *in vivo* treatment. Applicant argues that the polypeptide of the claims "has completely different physical and chemical characteristics from the protein of the '649 patent" and can be transduced into cells "within one hour" thus fulfilling a "showing of long felt need in the art" (page 11). While these arguments have been considered in full they are not found persuasive for the following reasons.

The '867 publication teaches a polynucleotide encoding a cell-permeable osteoinductive fusion polypeptide comprising: a) a polynucleotide encoding a cell-permeable polypeptide operatively linked to, b) a polynucleotide encoding an osteoinductive polypeptide, which when expressed together promote bone growth and disc regeneration in vivo. Specifically the reference teaches a fusion protein comprising at least one cell-permeable polypeptide including the instantly-elected HIV-TAT of the instant claims, operatively linked to at least one osteoinductive polypeptide, including

BMPs and/or TGF-β. The instant specification identifies SEQ ID NO: 1 as "a gene encoding hBMP2" (page 18, line 7). The '867 reference teaches that the fusion of BMP-2 with TAT allows for the polypeptides to permeate a cell membrane without cell membrane receptors (page 2, paragraph 0024).

The instant disclosure acknowledges that the '867 publication "discloses a fusion polypeptide of a bone morphogenetic polypeptide and a protein transduction domain (PTD), and a method for inducing bone formation in animals by administering the fusion polypeptide" (page 12, lines 21-23), but states that "even if PTD is used to introduce proteins into cells, it cannot be said that all the proteins are activated to show the expected bone morphogenetic potencies" (page 13, lines 3-4), and that the crux of the instant invention is that "the present inventors have found that the primary factor of the lack of efficiency in administering the previously known rhBMPs into living human beings or mammals is due to their biochemical activity" (page 14, lines 1-3).

The '867 publication does not teach a "furin activation domain" (FAD) comprising the instantly-elected SEQ ID NO: 14, which is defined within the instant specification as "a hBMP2 pro-domain" (page 18, line 10). The '649 Patent, however, teaches a nucleic acid sequence that is 99.2% homologous to the sequence of SEQ ID NO: 14 and SEQ ID NO: 1 combined. The '649 Patent teaches that this sequence comprise the full length of the pro-protein of human BMP-2. Furthermore, the Leighton et al. reference provides evidence that it was well-known within the art, prior to filing, that BMP proproteins are activated within the cell by furin and furin-like protein convertases at the amino acid motif RX(K/R)R (page18480, paragraph 4, lines 1-5). While the instant

SEQ ID NO: 1 encodes the hBMP-2 sequence following cleavage, it is the last amino acids of the "hBMP2 pro-domain" of SEQ ID NO: 14 that includes the R*X*(K/R)R protein convertase domain as taught by the Leighton reference. The Leighton reference teaches that expression of the proprotein with this cleavable R*X*(K/R)R domain is essential for BMP activity (line bridging pages 18482-18483). In the absence of this cleavable domain BMP protein is expressed and secreted but has no C-proteinase activity (Figure 4).

Examiner maintains that the instant claims are drawn to a polypeptide and not a method of making nor a method of stimulating the growth or formation of tissues, nor specifically bone or cartilage. Applicants arguments that the polypeptide of the claims is distinguished over that of the prior art is based upon the differences in the method of making and not to the structure of the sequences themselves. The prior art teaches the generic form of the claimed polypeptide and thus encompasses the polypeptide regardless of linear or 3-dimensional structure. The court has held that when the compound is not specifically named, if one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the elements included in the generic formula before any of the compounds can be "at once envisaged." *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). In the instant case, one of ordinary skill in the art can at once envisage within the prior art the fusion polypeptide comprising the requisite PTD, FAD, and TRD

elements and specifically wherein PTD equals TAT, FAD is the hBMP2 pro-domain of SEQ ID NO: 14, and the TRD is the BMP of SEQ ID NO:1.

Furthermore, Examiner maintains that the case law clearly states that something which is old does not become patentable upon the discovery of a new property.

> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Thus, the claiming of a new use, new function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Further, *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999). Applicants arguments that the "functional aspect of the claims polypeptide is an essential feature of all of the claimed polypeptides and compositions of the present application" (page 13, paragraph 1) and that the functional recitation "wherein the TRP permeates a cell membrane

without binding to a cell membrane receptor (new claim 29), structurally limit the claimed polypeptide are not found persuasive for the following reasons.

The '867 publication teaches a cell permeable fusion protein with the PTD-BMP elements of the claimed polypeptide but does not teach the FAD sequence. The Leighton et al. reference teaches that the FAD sequence comprising SEQ ID NO: 14 of the claims in tandem with the BMP comprising SEQ ID NO:1 forms the human BMP2 proprotein, which in combination is essential for protein activity. It would have been obvious to one of ordinary skill in the art to substitute the elements of the pro-BMP-2 sequence as taught by the Leighton reference into the TAT-BMP fusion protein as taught by the '867 publication. A skilled artisan would be motivated to combine the elements because it was known in the art that absent the "FAD" sequence (RX(K/R)R of SEQ ID NO:14) the TAT/hBMP-2 construct would be cell-permeable but would have no procollagen C-proteinase activity.

In *KSR International Co. v. Teleflex, Inc.,* the Supreme Court has stated that where there is a "pressure to solve a problem and a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense" (*KSR International Co. v. Teleflex, Inc.* 127 S. Ct. 1727, 82 USPQ2d 1385, Supreme Court, April 30, 2007). In the instant case, the prior art demonstrates that there are a finite number of ways to produce such a protein, and thus, the invention as a whole is *prima facie obvious*, if not actually anticipated by the references.

Conclusion

8. No Claim is allowed.

9. This application contains claims drawn to an invention nonelected with traverse in Paper filed on July 23, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-W and ALT F 5:30 to 3:30, TELEWORK-Thursdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/John D. Ulm/
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